REMARKS

The Office Action of April 8, 2008 has been reviewed and the comments therein carefully considered. Claims 32 and 102-126 are currently pending, of which claims 105, 109 and 113-125 were previously withdrawn as directed to non-elected species. Claims 32, 102-104, 106-108, 110-112 and 126 stand rejected under 35 U.S.C. §103(a) for obviousness over Rosenblum et al. (U.S. Pat. No. 5,846,966), The Medical Letter on Drugs and Therapeutics, 1998, Vol. 40, Issue 1030, pp. 68-69 ("Medical Letter") and Bergey et al. (EP 0 457 514). The rationale supporting this rejection is set forth at pages 4-6 of the Office Action. This rejection is respectfully traversed.

The present invention is directed to a triple combination treatment composition of a sterol absorption inhibitor (such as ezetimibe), a PPAR activator (such as fenofibrate), and at least one cardiovascular agent (such as an ACE-inhibitor like captopril).

Rosenblum et al. discloses that certain sterol absorption inhibitors, like ezetimibe, lower serum cholesterol levels and inhibit the intestinal absorption of cholesterol so as to significantly reduce the formation of liver cholesteryl esters and the risk of atherosclerosis. (Rosenblum, col. 20, lines 39-40).

Medical Letter teaches fenofibrate as useful in reducing VLDL cholesterol and triglycerides (Medical Letter, page 68). This reduction in triglycerides shifts the sub-group of LDL cholesterol to one that is less atherogenic. *Id.*

Bergey et al. is directed to a method for preventing, stabilizing, or causing regression of atherosclerosis by administering a combination of a cholesterol lowering drug, such as pravastatin, and an ACE inhibitor. (Bergey et al., Abstract). Bergey et al. cites a study from the American Journal of Hypertension in which it was discovered that captopril significantly reduced serum cholesterol and increased HDL. (Bergey et al., page 2, lines 17-19). Bergey et al. then asserts that there is no evidence that these therapeutic effects result from inhibition of the cholesterol synthetic pathway, and thus the therapeutic mechanism for ACE inhibitors is different from that of HMG CoA reductase inhibitors such as statins. (Bergey et al., page 2, lines 19-22). This finding serves as the motivation for Bergey's invention, in which an inhibitor of HMG CoA reductase is provided in combination with an ACE inhibitor. (Bergey et al., page 8, lines 18-22). According to Bergey et al., combination therapy of drugs known to have separate mechanisms of action is preferred over monotherapy since co-administration can produce a maximum therapeutic effect which is greater than can

be achieved when either drug is given alone. (Bergey et al., page 8, lines 34-43). Thus, according to Bergey et al., ACE inhibitors can be combined with cholesterol lowering drugs that inhibit cholesterol through a mechanism of action unique from the mechanism of action of ACE inhibitors to create a composition for treating atherosclerosis.

In the Office Action, it is contended that Rosenblum et al., Medical Letter, and Bergey et al. teach the benefit of ezetimibe, fenofibrate and captopril, respectively, in reducing serum cholesterol levels in patients. However, as admitted in the Office Action, none of these documents teach or disclose a triple combination therapy of ezetimibe, fenofibrate and captopril. Instead, the Office Action contends, one skilled in the art would find it obvious to combine these three compounds into the claimed triple combination therapy since, individually, they are each useful for the same purpose. (April 7, 2008 Office Action, pages 5-6).

However, Applicants submit that the claimed combination would not in fact be obvious to one skilled in the art in view of the documents of record. As described above, Bergey et al. teaches that ACE inhibitors like captopril should only be combined with other cholesterol-lowering drugs if the mechanisms of action of the two or more drugs do not overlap. In our case, the mechanism of action of ezetimibe was unknown at the time of Applicants' invention, as evidenced by a recent article from Expert Opinion on Pharmacotherapy attached as Exhibit A. In this article, published in 2007, the author states that "[t]he exact mechanism of action [of ezetimibe] is not yet fully elucidated." (Farnier, Expert Opin. Pharmacother. 2007, 8(9), page 1346). Thus, regardless of whether Bergey et al. teaches the usefulness of captopril alone in reducing serum cholesterol levels, one skilled in the art having read Bergey et al. would not find it obvious to combine ezetimibe and captopril, much less make the triple combination of ezetimibe, captopril and fenofibrate, absent an understanding of the mechanism of action of ezetimibe. Applicants are not claiming the compounds individually or even an atherosclerosis treatment regime comprising separate monotherapeutic administrations of each compound, but instead the subject claims are directed to a triple combination composition, and the evidence simply does not establish that one skilled in the art would have found this combination obvious.

Consequently, Applicants submit that the claimed composition is not obvious in view of the cited art and respectfully requests that the outstanding rejections of claims 32, 102-104, 106-108, 110-112 and 126 be reconsidered and withdrawn.

Double Patenting Rejection

In addition to the rejection under 35 U.S.C. §103(a) discussed above, claims 32, 102-104, 106-108, 110-112 and 126 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-7 and 17-20 of co-pending United States Patent Application Serial Number 11/897,227, which is a continuation of the subject application, in view of EP 0 457 514. Applicants respectfully disagree with and traverse this rejection. However, to expedite prosecution, a Terminal Disclaimer is submitted with this response to terminally disclaim the terminal part of the statutory term of any patent granted on the present application that would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §154 to 156 and 173 of U.S. Patent Application No. 11/897,227 subject to the conditions noted in the Terminal Disclaimer. The filing of the Terminal Disclaimer over U.S. Patent Application No. 11/897,227 overcomes the basis for rejection, therefore Applicants respectfully request that this rejection be reconsidered and withdrawn.

CONCLUSION

For all of the foregoing reasons, Applicants submit that pending claims 32 and 102-126 are patentable over the cited references and are in condition for allowance. Accordingly, reconsideration of the rejections and allowance of pending claims 32 and 102-126 are respectfully requested.

Respectfully submitted,
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